Pulmonary and Systemic Vascular Response to Continuous Infusion of 5-Hydroxytryptamine (Serotonin) in the Dog

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ABSTRACT
RUDOLPH, ABRAHAM M. AND MILTON H. PAUL. (Harvard Med. School and Children's Med.-Ctr., Boston, Mass.) Pulmonary and systemic vascular response to continuous venous infusion of 5-hydroxytryptamine were studied in eight dogs. Chronic catheterization of the pulmonary artery, aorta, and in some animals, the left auricle, permitted repeated studies in the same animal. Infusion rates as low as 20 μg/kg/min. of serotonin creatinine sulfate resulted in a twofold increase of pulmonary arterial pressure. In 11 experiments with an infusion rate of 150 μg/kg/min. there was a 300% increase of mean pulmonary pressure, a 28% drop in systemic arterial mean pressure, and a 60% rise of cardiac output. Calculated pulmonary resistances markedly increased to 500% of control levels, but in contrast, systemic resistances decreased by 55%. 5-Hydroxytryptamine is a powerful vasoconstrictor of the pulmonary vessels and a vasodilator of peripheral vessels, when administered by continuous infusion, and these effects persist as long as the drug is administered. The possible role of 5-hydroxytryptamine in production of pulmonary hypertension in congenital heart disease is considered.

The pulmonary circulation has generally been regarded as being particularly unresponsive to most factors affecting the systemic vasculature (1). Many factors such as exercise (2), anoxia (3) and various drugs (4), which have profound effects on peripheral small vessels, produce insignificant changes in pulmonary vascular resistance. During the course of our investigation of the effects of various substances on pulmonary vasculature, the powerful vasoconstrictor effect of 5-hydroxytryptamine was observed. The existence of a vasoconstrictor substance in serum had long been suspected. Rapport, Green and Page (5) isolated a vasoconstrictor principle, which they named serotonin, and Rapport identified this as 5-hydroxytryptamine (6). This substance has been purified and is stable in combination with creatinine sulfate.

The pulmonary hypertensive effect of serum (7), partly purified vasoconstrictor principle (8) and of pure serotonin (9, 10), has been repeatedly observed. Many of these studies have been carried out in isolated perfused lungs, and in all these investigations the effect of single injections over a very short period have been observed.

This report concerns the study of the effects of continuous infusion of 5-hydroxytryptamine into the venous system of intact anesthetized dogs. Pulmonary and systemic blood pressures, and occasionally left atrial pressures, were continuously recorded, and repeated determinations of cardiac output made, to assess the effects on vascular resistance in the greater and lesser circulations.

MATERIAL AND METHODS
Eight mongrel female dogs weighing 15-17 kg were used in this study. In three dogs, polyvinyl catheters
were inserted into the pulmonary artery, aorta and left auricle through a left thoracotomy; the chest was closed and the lung re-expanded (11). Experiments were conducted after a 10-day recovery period.

In the remaining five dogs, polyvinyl catheters were inserted into the pulmonary artery and right auricle, and into the carotid artery, and maintained for several months (12). Using this preparation it was possible to perform experiments on the same animal over the course of several weeks or months.

Vascular pressures were measured with Statham pressure transducers or Sanborn capacitance manometers and recorded with a multichannel direct-writing oscillograph. Cardiac output was measured by either the Fick method, or by the dye dilution technique, with continuous recording by a whole-blood densitometer (13). Blood oxygen saturation was measured by a spectrophotometric method (14). In the instances where oxygen was administered, blood oxygen content was determined by the manometric method of Van Slyke and Neill.

Oxygen consumption was measured by collection of an expired gas sample in a Douglas bag, and oxygen gas tensions of inspired and expired air were measured with a Beckman oxygen analyzer. During breathing of 100% oxygen, oxygen consumption was measured by the Benedict-Roth spirometric method.

The individual experimental procedure was conducted as follows: pentobarbital sodium was slowly administered through the right auricular or pulmonary arterial catheter in a dose of 35-40 mg/kg body weight. An intratracheal tube with a rubber cuff was inserted and the cuff was well inflated to avoid air leak. In view of the usual irregular respiratory response and bronchospasm usually induced by serotonin (14), accurate measurements of oxygen consumption could not be obtained unless a constant-volume respiratory pump was used. A Palmer pump, with a stroke volume of 200-250 ml and a frequency of 16/min. was employed to produce a regular respiratory cycle. Oxygen consumption during administration of 100% oxygen was effected by connecting the inlet and outlet tubes of the respiratory pump to a recording spirometer filled with oxygen. In one experiment serotonin was infused in the unanesthetized dog and systemic and pulmonary pressure responses were recorded without measurement of cardiac output.

After control pressure measurement and cardiac output determination, the infusion of serotonin was commenced. Serotonin creatinine sulfate solution (0.2 mg/ml in isotonic sodium chloride) was then infused at varying rates, from 20 µg/kg/min. to 200 µg/kg/min., but in most experiments 150 µg/kg/min. was infused. This latter dose is equivalent to 65 µg/kg/min. of serotonin base. After stabilization of pulmonary and systemic pressures, several determinations of cardiac output were made, the infusion being continued for 30-60 minutes. In some instances 100% oxygen was administered during infusion to assess its effect. After cessation of serotonin administration the cardiac output was again measured after the pressures had returned to near-control levels.

**RESULTS**

**Pulmonary Pressure.** The average control pressures recorded in the pulmonary artery were 14/5 mm Hg, and mean pressures ranged from 7 to 15 mm Hg with an average of 10 mm Hg. In every experiment there was a rise in pulmonary arterial pressure after serotonin administration. The rise in pressure occurred rapidly, starting within 2-3 seconds after the onset of the infusion, and reaching a maximum in 30-60 seconds (fig. 1). The pressure was maintained as long as the same rate of infusion continued. Infusions were continued for periods of 30-60 minutes, and in no instance was tachyphylaxis, as reported with single injection (15), encountered.

The degree of pressure rise varied with the rate of infusion of serotonin. An infusion rate as low as 20 µg/kg/min. of serotonin creatinine sulfate, equivalent to 9 µg/kg/min. of serotonin base, resulted in a definite rise of pulmonary pressure, with an increase of the mean pressure to almost double control levels. Increasing the rate of infusion resulted in a stepwise increase in pulmonary pressure, to a maximum of about 4-5 times control mean pressure, with an infusion rate of 150 µg/kg/min. of serotonin creatinine sulfate. The pressure was increased to an average of 72/28 mm Hg. The mean

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*Serotonin creatinine sulfate was generously supplied by Upjohn Co.*
pressure rose to 27–53 mm Hg with an average of 41 mm Hg, corresponding to a 300% rise over control levels. Further increase in the infusion rate resulted in no further rise in pulmonary arterial pressure.

After cessation of the serotonin infusion, the pressure in the pulmonary artery dropped quite slowly. The pressure began to fall off within a few seconds and returned to control levels in 8–30 minutes. The time taken for the mean pressure to return to control levels varied considerably in individual experiments, and in some instances had not quite reached these levels 30 minutes after infusion was stopped. In the unanesthetized dog similar pressure responses were observed in both the pulmonary and systemic circulations.

**Systemic Arterial Pressure.** The average control systemic arterial pressure was 125/91 mm Hg, and mean pressures ranged from 80 to 134 mm Hg with an average of 105 mm Hg.

Three different types of immediate response to serotonin infusion were noted (fig. 2). In three experiments systemic hypertension occurred, followed after 1–2 minutes by a fall to hypotensive levels. In seven experiments, an immediate hypotension followed by a small rise, and then a slow fall, was noted. In two experiments, immediate hypotension, which persisted, was observed. Within 1–3 minutes, the systemic pressure had dropped in all experiments to an average level of 45/45 mm Hg. The mean pressure dropped to 76 mm Hg (a 28% fall) with a range of 40–95 mm Hg. Associated with these changes was a marked increase of pulse pressure from a control of 37 mm Hg to 64 mm Hg during serotonin infusion. The systemic arterial pressure returned to control levels within 8–30 minutes after the infusion was stopped, except in two experiments, where it was still decreased after 30 minutes.

**Left Atricular Pressure.** This was measured in three dogs, and showed no significant changes with serotonin (fig. 3). The control mean pressure of 6 mm Hg rose by 1 mm Hg during serotonin infusion in 3 dogs. We have therefore assumed that in all experiments where left atricular pressure was not measured the control level was 6 mm Hg, and that pressure did not alter significantly during administration of serotonin.

**Cardiac Output, Heart Rate and Stroke Volume.** With low infusion rates the cardiac output rose 10–50% above control levels. With an infusion rate of 150 µg/kg/min. the average control output was 2.7 l/min. and the average rise was 1.7 l/min. or 60%. Similar increases in cardiac output with serotonin were obtained using either the indicator dilution or the Fick technique.

Heart rate was increased during serotonin administration in all experiments. The average control rate was 132/min. and during serotonin infusion it increased to 168/min. An occasional transient bradycardia was observed in the 1st minute of the infusion. Stroke volume showed a variable response; in five experiments it increased, in two it decreased, and in four experiments there was no change.
in stroke volume. Cardiac output decreased after cessation of the infusion, and usually returned to control levels in 8–30 minutes, but in some instances it was still elevated after 30 minutes.

Calculated Pulmonary and Systemic Vascular Resistance. Pulmonary vascular resistance was calculated on the assumption that left auricular pressure did not alter significantly during serotonin administration. Evidence for the validity of this assumption has been presented. All calculations assumed a left intraauricular pressure of 6 mm Hg. During the control period, pulmonary vascular resistance ranged from 0.4 to 2.8 mm Hg/l/min., with an average of 1.5 mm Hg/l/min. The resistance rose to moderate levels (2–3 times control) with slow infusion and with more rapid infusion (150 μg/kg/min.) increased to levels of 3.3–17.7 mm Hg/l/min. with an average of 8.9 mm Hg/l/min., a rise of 500%. The pulmonary vascular resistance usually reached levels one-third to one-half the calculated systemic vascular resistance; in one instance it actually exceeded the systemic resistance. The pulmonary resistance dropped rapidly after infusion was stopped, but in most instances was still slightly elevated above control levels after 8–30 minutes.

In contrast to the significant rise of pulmonary vascular resistance, systemic vascular resistance dropped markedly from control levels of 24.5–61.7 mm Hg/l/min. with an average of 39.6 mm Hg/l/min. to 7.4–28.6 mm Hg/l/min. with an average of 17.8 mm Hg/l/min. during serotonin infusion, a 55% decrease. In one experiment, it dropped to 20% of control, to a level lower than the pulmonary resistance. After cessation of serotonin, systemic vascular resistance rose slowly, but in most cases had not completely returned to control levels after 8–30 minutes.

Arterial Oxygen Saturation. Arterial saturation under the experimental conditions ranged from 90–97% in the control periods. In one animal, arterial oxygen saturation dropped to 60% in two separate experiments during serotonin infusion. In most other experiments the saturation dropped moderately by 8–10%. In one experiment (dog 1, 6/2/56) due to poor ventilation by the respiratory pump, the control saturation was only 75–80%, and this dropped to 55% during serotonin administration.

Effects of Breathing 100% Oxygen. In view of the observed drop in arterial oxygen saturation in many experiments during serotonin administration, and the knowledge that hypoxia causes an increase in pulmonary arterial pressure, the effect of breathing 100% oxygen on pulmonary arterial and systemic arterial pressures, cardiac output and pulmonary and systemic resistances was studied in four experiments during serotonin infusion. It was observed that oxygen administration produced a definite reduction of pulmonary arterial pressure in all instances. This was, however, quite small, and the mean pressure dropped by only 3.5 mm Hg. Cardiac output,
pulmonary vascular resistance, and systemic vascular resistance were not altered significantly, in spite of the return of oxygen saturation to control levels during 100% oxygen administration.

**DISCUSSION**

Numerous observations on the effects of serum vasoconstrictor or purified serotonin have revealed a pulmonary hypertensive response to intravenous administration. Previous studies, however, have been concerned with the effects of single injections. The right ventricular systolic (14) or pulmonary arterial pressures (9, 16, 17) rose rapidly after the injection, and the hypertensive response has been reported to be 10-20 times greater than that of epinephrine (16). The pulmonary hypertension was assumed to be due to a vasoconstrictor effect but simultaneous flow measurements were not made. MacCanon and Horvath (18) studied flow during single injections using a radioactive indicator dilution technique, and found a small rise in cardiac output. Page (19) found that stroke volume and minute volume, as measured from pulse pressure contours, were nearly doubled. These studies, however, analyzed the responses in the rapidly changing hemodynamic status after single injection. Our studies with continuous infusion of serotonin revealed a significant increase in cardiac output, as measured by both the Fick and dye dilution methods. The cardiac output rose 60% above control levels and was associated with an increase in heart rate.

The marked pulmonary hypertension produced by serotonin is of great interest in view of the limited reactivity of the pulmonary vasculature to most other mechanisms studied. The rise in pulmonary pressure occurs immediately after injection of the drug into the pulmonary artery and is probably due to a direct local effect on small pulmonary vessels. The observed pulmonary hypertension is in part related to the rise in cardiac output, which consistently occurs during continuous infusion, but the considerable increase of pulmonary vascular resistance indicates that the main mechanism is vasoconstriction.

Arterial oxygen saturation is usually considerably reduced during serotonin infusion. Since hypoxia is known to produce a rise of cardiac output (3) and possibly an increased pulmonary vascular resistance (20, 21), the effects of oxygen breathing were studied. In spite of the fact that the oxygen saturation returned to near-control levels, the pulmonary vascular response and cardiac output response to serotonin were unaltered.

A nervous reflex mechanism for the production of pulmonary vasoconstriction is unlikely, in view of the studies of Comroe et al. (14) and our own observations on the effects of single injections. Reflexes arising from the aorta, coronary vessels and carotid nerves do not play a part in the pulmonary vascular response, since injections of serotonin into the left auricle do not result in pulmonary arterial hypertension. The possible role of reflexes arising within the lungs themselves has not been eliminated. Serotonin has a marked constrictor effect on smooth muscle from various sources (22-24) and it seems likely that the pulmonary vasoconstrictor action is a direct local effect.

In contrast to the consistent and marked rise in pulmonary arterial pressure, the systemic arterial pressure has been reported to show variable responses to single injection. We, however, have noted a consistent reduction in systemic pressure during continuous infusion of serotonin, after an initial variable response. This decrease may be very marked, so that in one instance systemic mean pressure was lower than pulmonary arterial mean pressure. This reduction of arterial pressure, in the face of a rise in cardiac output, signifies a considerable decrease of peripheral resistance, which is unexpected in view of the marked constrictor effect of serotonin on smooth muscle. Even in vivo studies have shown a powerful local vasoconstrictor effect on the smooth muscle of the vessel of the rabbit ear (25). This peripheral vasodilator effect of continuous infusion in the intact animal requires explanation.

Page and McCubbin (26) have mentioned a possible action of 5-hydroxytryptamine that blocks or reduces neurogenic vasoconstriction. They found that in normotensive dogs pretreated with ganglion-blocking drugs there was a marked hypertensive response to 5-hydroxytryptamine. They believe that the
direction and intensity of the response depends largely on the degree of vasoconstrictor tone already present.

Feldberg and Smith (27) consider that 5-hydroxytryptamine is one of the drugs capable of releasing histamine and it is possible that the vasodilator effect is due to histamine release.

Single injections of 5-hydroxytryptamine into the venous system result in a series of reflex responses—apnea, bradycardia and hypotension (14) which are similar to those seen with other drug injections that elicit the von Bezold-Jarisch effect. The hypotension observed after single injection was thought to be related to bradycardia (14) or to a decrease in cardiac output resulting from pulmonary vasoconstriction (19). These mechanisms which have been proposed to explain the initial hypotension, certainly play no role in the persistent hypotension observed during continuous infusion, since tachycardia and increased cardiac output occurred in all our studies.

5-Hydroxytryptamine has a more powerful vasoconstrictor effect on pulmonary vessels than any other drug of neural reflex that has been studied. Comroe has suggested that the hemodynamic and respiratory changes associated with pulmonary embolism may be related to serotonin released from clotted blood. It is also possible that this substance plays a role in the production of pulmonary hypertension in congenital heart disease associated with shunting of blood from the systemic to the pulmonary circulation. Pulmonary hypertension occurs more commonly with ventricular septal defect and patent ductus arteriosus in which there is a considerable turbulence, as evidenced by loud heart murmurs. It is possible that this turbulence results in platelet disruption, which releases 5-hydroxytryptamine into the pulmonary circulation.

REFERENCES